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Synthesis, Characterisation and Spectral Studies of Metal Complexes of Glimepiride, An Oral Antidiabetic Drug

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ABSTRACT

Metal complexes of manganese (II) and cobalt (II) have been synthesized with active hypoglycemic agent (glimepiride), an oral antidiabetic drug. The elemental analyses of the ligand as well as metal complexes indicate that complexes having 2:1 stoichiometry of the type $(C_{24}H_{34}N_4O_5S)_2 M \cdot 2H_2O$, where M= Mn(II) and Co(II). The complexes have been characterized by IR spectra, electronic spectral and molar conductance data. Infrared spectral studies confirm the co-ordination of sulphonyl oxygen on one side and enolic oxygen attached from other side with the metal ion. On the basis of electronic spectral values the complexes are proposed to have octahedral geometry. The molar conductivity also reveals that the complexes are non-ionic in nature.

Key words: Glimepiride; Synthesis, Characterization; Metal Complexes; Infrared spectroscopy.

INTRODUCTION

A perusal of available literature shows that systemic study on complexation of metals with sulphonyl ureas is carried out by Iqbal and coworkers. The study of chemistry and chemical reaction of co-ordination compound helps in establishing structure-activity relationship. It has been reported that in biological activity metal complex is more potent and less toxic as compared to the free ligand⁵⁻⁶. or in other words many drugs possessed modified pharmacological and toxicological properties when administered in the form of metallic complexes. Probably the most

widely studied metals in this respect are Mn(II), Co(II), Fe(II), Cr(II) and Cu(II), since a host of low molecular weight these metal complexes had been proven beneficial against several diseases such as *Diabetes mellitus*, tuberculosis, gastric ulcers and cancers⁷⁻⁸.

Glimepiride, 1-(p-(2-(3-ethyl-4-methyl-2-oxo-3-pyrrolin-1-carboxamido)ethyl)phenyl)sulfonyl)-3-(trans-4-methylcyclohexyl) urea is a third generation hypoglycemic drug which is potent in the treatment of non-insulin dependent *diabetes mellitus* (NIDDM)¹⁻² Glimepiride is a white crystalline powder, relatively insoluble in water.

Glimepiride exhibits slow gastrointestinal absorption rate and inter individual variations of its bioavailability³. The slow absorption rate of drug usually originates from either poor dissolution of drug from the formulation or poor permeability across gastrointestinal membrane. For poorly water soluble and highly permeable (class II) drugs the rate of oral absorption is often controlled by the dissolution rate in the gastrointestinal tract⁴. Complexation of sulphonyl ureas with transition metals has been

studied in detail by Yoshinaga & Yamamoto (1966) and Iqbal *et al.*,²³⁻²⁹ However, in view of the above and in continuation of our work, it is interesting to have an insight into the synthesis of Mn(II) and Co(II) complex with Glimepiride and to diagnose various structural aspects of the isolated complex. Here the synthesis and characterization of manganese and cobalt, first transition metals complex with glimepiride has been described

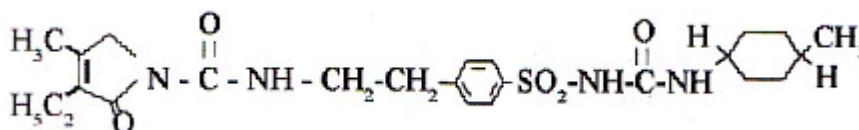


Fig. 1: Structure of glimepiride

EXPERIMENTAL

Ligand-metal ratio

- Pure Glimepiride (I) (Trade name, Amaryl) 1-((P - (2 - (3 - ethyl - 4 - methyl - 2 - oxo - 3 - pyrroline - 1 - Carboxamido) ethyl-cyclohexyl) Urea supplied by Ipca laboratories limited, Ratlam in powdered form, m.p. 207°C 0.005 M and Mn(II), Co(II) ($\text{MnCl}_2 \cdot 4\text{H}_2\text{O}$ and $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$) 0.01 M (Analar grade) both were prepared in purified 80% ethanol. Glimepiride (20mL) was diluted to .200 mL and titrated conductometrically against manganese (II) chloride and cobalt(II) Chloride at $27 \pm 1^\circ\text{C}$. Results were plotted in the form of a graph which indicate the ligand metal ratio as 2:1.
- Formation of complex ion in 2:1 (L2M) ratio was also confirmed by Job's method⁹ of continuous variation as modified by Turner and Anderson¹⁰ using Δ conductance as index property. From these values the stability constant ($\log k$) and free energy change ($-\Delta F$) were also calculated.

Synthesis of complex

The chemicals used in this synthesis were all of analytical grade. A weighed quantity of glimepiride (2 mol) was dissolved in minimum quantity of 80% DMF. The chlorides of manganese and cobalt were prepared by dissolving it separately in the same solvent. Ligand solution was added

slowly with constant stirring into the solution of metallic salt at room temperature maintaining the pH between 7 to 8 (for Mn(II)) and 8 to 8.5 (for Co(II)) by adding dilute NaOH solution. On refluxing the mixture for 3h. at 75°C and 80°C and on cooling, the complex separated out, which was filtered off, washed well with DMF (80%) and finally dried in vacuum and weighed.

The elemental analysis of the isolated complex were carried out using the reported methods¹¹⁻¹⁵.

The metal was estimated by titration against standard EDTA solution at a suitable pH using the suitable indicator¹⁶. The IR spectra of the ligand as well as of the complex was recorded on Perkin Elmer spectrophotometer at ($4000-450\text{cm}^{-1}$) (CDRI Lucknow), Electronic spectra of the above mentioned ligand and isolated complex was recorded on a λ 25 instrument model at scan speed 480.00 nm/min. (Sadhu Vaswani College, Bairagarh, Bhopal)

RESULTS AND DISCUSSION

Infrared spectral studies of the complex

The synthesized complexes are brownish black and green crystals is characterised for manganese and cobalt complex. They are stable and soluble in dilute alkali, DMSO, pure acetone, pure methanol etc, insoluble in water and all other

Table 1: Synthesis and physicochemical characteristics of complexes

Ligand and Complex	Ligand/Metal Ratio	Colour	% yield	Stability constant logk (L/mole)	Free energy change ΔF (K.Cal/mole)
GLIM-pure drug	-	White powder	-	-	-
(GLIM) ₂ Mn	2:1	Brownish black	68%	11.57	-15.62
(GLIM) ₂ Co	2:1	Green crystals	40%	12.72	-17.17

Table 2: Analytical data of the complex

Ligand / Complex	Elemental analyses found (calculated)					m.p. °C
	C	H	N	S	Metal	
C ₂₄ H ₃₄ N ₄ O ₅ S	58.60 (58.65)	7.20 (7.22)	11.31 (11.35)	6.49 (6.51)	-	207
(C ₂₄ H ₃₄ N ₄ O ₅ S) ₂ Mn	38.91 (38.51)	5.42 (5.78)	9.11 (8.99)	6.62 (6.85)	11.18 (11.55)	218
(C ₂₄ H ₃₄ N ₄ O ₅ S) ₂ Co	36.67 (36.78)	5.41 (5.11)	8.91 (8.58)	6.12 (6.54)	11.79 (12.06)	210

Table 3: IR Absorption data of the complexes in cm⁻¹

Ligand and Complex	$\nu(\text{NH})$	$\nu(\text{C=O})$	$\nu(\text{S=O})$	$\nu(\text{M-O})$	$\nu(\text{SO}_2\text{N})$	$\nu(\text{H}_2\text{O})$
Ligand and complex (C ₂₄ H ₃₄ N ₄ O ₅ S)	3288	1706	1394	-	1155	-
Complex (C ₂₄ H ₃₄ N ₄ O ₅ S) ₂ Mn.2H ₂ O	-	1701	1353	670	1162	3379
Complex (C ₂₄ H ₃₄ N ₄ O ₅ S) ₂ Co.2H ₂ O	3286	1703	1357	672	-	3687

organic solvents. The IR spectra¹⁷⁻²¹ of the ligand and the isolated complex were recorded in the range 4000-450 cm⁻¹ and the probable assignments are given in Table 3. The proposed structure for the isolated complex is also supported by IR absorption bands and characterized by the absorption of carbonyl (C=O) group at 1701 cm⁻¹ and 1703 cm⁻¹ in Mn(II) and Co(II) ligand complex respectively. Also the NH group observed at 3288 cm⁻¹ in the ligand glimepiride shifted to 3286 cm⁻¹ in cobalt glimepiride complex. While in the case of manganese glimepiride complex the band frequency is just disappear.

The next IR band of structural significance of the ligand appears at 1394cm⁻¹ which may be assigned to $\nu\text{S=O}$ which got shifted downward at 1353 cm⁻¹ in manganese glimepiride complex while in cobalt ligand complex it just appears at 1357 cm⁻¹ respectively, The shift of the $\nu\text{C=O}$ and $\nu\text{S=O}$ by decreased frequencies in the complex indicates that these groups are involved in the complexation. The linkage through amide -O- and sulphone -O- atom was further supported by the appearance of a band in the far IR region at 670 cm⁻¹ and 672 cm⁻¹, in the Mn(II) and Co(II) complex that may be

assignable to M-O frequency²². Additional band in the complex region of Mn(II) and Co(II) at 1447 cm^{-1} and 1430 cm^{-1} compared with IR spectra of free ligand has tentatively been assigned to six membered enolic ring structure modified to chelate ring formation in complex²³⁻²⁶. A strong band in the region of 3379 cm^{-1} and 3687 cm^{-1} indicates the presence of co-ordinated water for Mn-glime complex and Co-glime complex respectively.

Electronic spectral studies of complexes

The diffused reflectance spectrum of the Mn (II) complex shows three bands at 24,390, 22,220 and 16,666 cm^{-1} which can be assignable to ${}^4E_g(G) \leftarrow {}^6A_1g$, ${}^4T_2g(G) \leftarrow {}^6A_1g$ and ${}^4T_1g(G) \leftarrow {}^6A_1g$ transitions, respectively suggesting an octahedral environment around the manganese ion. The electronic spectrum of the Co(II) complex

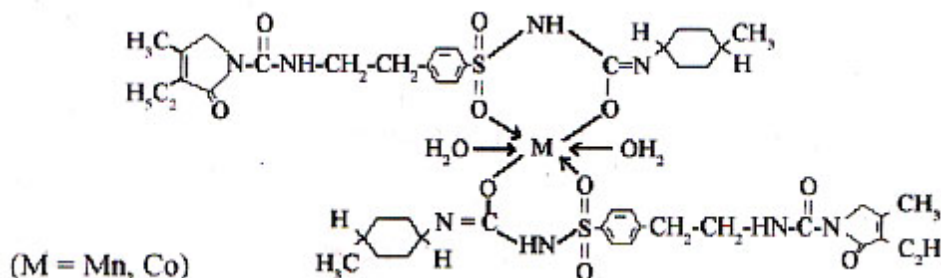


Fig. 2: Structure of glimepiride metal complex

with the formula $(\text{glim})_2\text{Co}2\text{H}_2\text{O}$ gives three bands at 14,990, 17,420 and 22,250 cm^{-1} . The bands observed are assigned to the transitions ${}^4T_1g(F) \rightarrow {}^4T_2g(F)$ and ${}^4T_1g(F) \rightarrow {}^4A_2g(F)$ and ${}^4T_1g(F) \rightarrow {}^4T_2g(P)$ respectively, suggesting the presence of Co(II) complex in octahedral geometry²⁷⁻²⁹. The region at 25,660 cm^{-1} refers to the charge transfer band.

CONCLUSION

From the present study, it can be concluded

that the study of chemistry and chemical reaction of co-ordination compounds helps in establishing structure activity relationship and it has also been observed that in biological activity metal complex is more potent and less toxic as compared to the free ligand.

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